METHODS AND SYSTEMS FOR PROMOTING INTERACTIONS BETWEEN PROBES AND TARGET MOLECULES IN FLUID IN MICROARRAYS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. patent applications Ser. No. 60/327,686, entitled "Methods and Apparatus for Microarray Hybridization" by Shiping Chen et al., filed Oct. 4, 2001, and Ser. No. 60/402,371, entitled "Micro-Channels for Hybridization Enhancement" by Shiping Chen, filed Aug. 8, 2002. The above applications are incorporated by reference herein in their entireties as if fully set forth below for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates generally to the field of biochemical analysis in which it is desirable to facilitate interaction between immobilized probes with target molecules in a fluid.

BACKGROUND OF THE INVENTION

[0003] Many applications in bio-chemical study involve the binding of target molecules in a target liquid to probes that are immobilized on a substrate surface. The immobilized probes can be, for example, oligonucleotides, peptides, polypeptides, proteins, antibodies, or other molecules capable of reacting with the target molecules.

[0004] **FIG. 1** shows one widely used apparatus for microarray hybridization experiments. A cover slip having small risers provided on each edge is placed on a microscope substrate slide, on which the microarray probes are deposited. The target sample is introduced into the space between the cover slip and the substrate slide, and this assembly is then sealed in a small chamber, which is then placed in a water bath and maintained at a constant temperature for several hours.

[0005] An advantage of such a hybridization device is its low cost and simplicity. However, it also has several disadvantages. First, the sensitivity of the system may be limited. The narrow space between the cover slip and the substrate (typically 20 μm to 50 μm in height) restricts the flow of sample fluid and limits the mobility of target molecules. For any individual probe in the microarray, only complementary target molecules that are within a small area centered around the probe spot are likely to hybridize with the probe. As shown in **FIG. 2**, the actual effective sample volume for any probe can be expressed as $v=\pi r^2 h$, where r is the radius of the above mentioned area centered around the probe spot and h is the height of fluid space between the cover slip and the substrate. Such a volumetric restriction can significantly reduce the sensitivity of the detection. Assuming a typical r of 200 μm and the entire cover slip area of 20 mm×20 mm, the effective volume is only 0.03% of the total volume. This means that the detection sensitivity is reduced by a factor of 3000.

[0006] Another possible disadvantage is that there can be variation of hybridization sensitivity between chips. The amount of target molecules available for hybridization is proportional to the volume of sample fluid in the effective space described above and the effective sample volume is in turn proportional to the height of the gap between the slip and substrate. Because it is very difficult to precisely control the gap height, the chip-to-chip hybridization consistency can be low with this method.

[0007] In addition, the hybridization process can be slow. Because the sample fluid is quiescent, the target molecules rely on random Brownian motion to meet and hybridize with complimentary probes. This can result in a very long hybridization process (usually overnight).

SUMMARY OF THE INVENTION

[0008] In accordance with embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a substrate having an array of probes deposited on a surface of the substrate for interaction with a target molecule in a target liquid; and a cover coupled to the substrate to form a reaction chamber therebetween, wherein the array of probes is contained within the reaction chamber and the substrate and the cover are movable relative to each other.

[0009] In accordance with further embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a reaction chamber having an interior cavity and an array of probes deposited on an inner surface of the interior cavity for reaction with a target molecule in a target liquid; a magnetically reactive mixing member contained in the reaction chamber; and a magnetic field generator for moving the magnetically reactive mixing member through the target liquid.

[0010] In accordance with further embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a reaction chamber having an interior cavity; a target liquid contained within the interior cavity of the reaction chamber; a volume exclusion liquid contained within the interior cavity; and an array of probes deposited on an inner surface of the interior cavity of the reaction chamber for reaction with a target molecule in the target liquid.

[0011] In accordance with further embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a reaction chamber having an interior cavity; an array of probes deposited on an inner surface of the interior cavity for reaction with a target molecule in a target liquid; and a transducer for directing acoustic waves into the interior cavity of the reaction chamber.

[0012] In accordance with further embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a reaction chamber having an interior cavity; an array of probes deposited on an inner surface of the interior cavity for reaction with a charged target molecule in a target liquid; and a voltage generator for generating a voltage across the interior cavity to move the charged target molecule.

[0013] In accordance with further embodiments of the present invention, a microarray apparatus is provided. The apparatus comprises a reaction chamber having an interior cavity; an array of probes deposited on an inner surface of the interior cavity for reaction with a charged target molecule in a target liquid; and a temperature control mecha-